

REMARKS

II. Patentability Arguments

A. The Rejections Under 35 U.S.C. § 102(e) Should Be Withdrawn

Claims 22-29 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Iverson (U.S. Patent No. 5,236,825, "Iverson"). The rejection should be withdrawn because the reference fails to teach every limitation of the present claims.

The Examiner has characterized the instant claims as being product-by-process claims. However, the Examiner has limited his examination to the product alone. In so limiting the examination the Examiner is ignoring explicit limitations of the claims, which the applicants believe should properly be considered when examining any claim. When the instant claims are properly viewed in their entirety, including all of the recited limitations, the applicants submit that they are novel over the art referred to by the Examiner because no single piece of prior art teaches each and every element of the present claim as is required under the law to properly anticipate an invention.

The Examiner interpreted the instant claims as "being drawn to a combination of polypeptides comprising V_H and V_L, which in combination exhibit catalytic activity."

The Examiner has characterized Iverson as teaching catalytic antibodies. The Examiner is invited to note that the antibody taught by Iverson is a catalytic antibody which was made by the standard hybridoma approach.

Further, the present invention is concerned with a catalytic antibody produced by a synthetic method in which a genetic library is generated and represents the immune repertoire of an animal. More specifically, the present invention provides a catalytic antibody by a method in which a large number of different antibody variable region genes (i.e., V_L and V_H) is cloned and expressed in expression vectors. The inventors described and used a set of DNA primers which are capable of hybridizing to a much larger number of antibody genes allowing amplification of these genes using PCR which results in a genetically diverse population of V_H or V_L coding sequences.

Since Iverson does not teach each and every element of the instant invention as presently claimed, Iverson cannot properly anticipate the instant invention. Therefore, the applicants respectfully submit that the rejection over Iverson is improper and should be withdrawn.

Claims 22-29 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Schochetman (U.S. Patent No. 4,888,281, "Schochetman"). The rejection should be withdrawn again because the reference fails to teach every limitation of the claimed invention.

The Examiner has characterized Schochetman as teaching catalytic antibodies. However, Schochetman teaches a mouse monoclonal antibody with catalytic activity made by hybridoma technology.

The Examiner has characterized the instant claims as discussed above. The product claimed by the instant invention is a V_H and V_L polypeptide which in combination has a catalytic activity and is made by the synthetic process described above which differs from that disclosed by Schochetman

Since Schochetman does not teach every element of the instant invention, Schochetman does not anticipate the instant invention. Hence, the applicants respectfully submit that the rejection over Schochetman should be withdrawn.

Claims 22-29 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Kim (U.S. Patent No. 4,792,446, "Kim"). Because the reference does not teach every limitation of the present invention the rejection should be withdrawn.

The Examiner has characterized Kim as teaching catalytic antibodies. Kim teaches catalytic antibodies only for a particular type of chemical reaction. Further, Kim teaches that the catalytic antibodies are produced by inducing an immune response in an animal. In contrast, the induction of an immune response is not utilized in the practice of the present invention which as discussed above is a V_H and V_L polypeptide which in combination have a catalytic activity and which are made by an explicitly recited synthetic method.

Since Kim does not teach every element of the instant invention, Kim cannot properly anticipate the instant invention. Therefore, the applicants respectfully submit that the rejection over Kim should be withdrawn.

In view of the foregoing arguments, the Applicants respectfully submit that the rejections under 35 U.S.C. § 102(e) should be withdrawn.

B. The Rejections Under 35 U.S.C. § 112, first paragraph, Should Be Withdrawn

The Examiner rejected claims 22-29 under 35 U.S.C. 112, first paragraph, alleging inadequate written description of the claimed invention. According to the Examiner, "the claimed invention is drawn to a very broad genus, i.e., essentially any catalytic antibody. One can not know the structure of such a catalytic antibody *a priori*... Merely to set forth the function and the general class of macromolecule is not sufficient to have conveyed to one of skill in the art that applicants had a representative number of species from this genus in their possession at the time of filing."

The present claims are directed to a catalytic antibodies made by the recited process. The structure of any of the antibodies generated by the recited method was not known *a priori* and this did not prevent the applicants from generating and identifying any of the antibodies. In fact, it is common practice in the field of the antibody production to generate an antibody without knowing its structure *a priori*. Furthermore, it is common practice in the field of antibody production to characterise antibody by its ability to bind a particular target (antigen). The Examiner is invited to note three major points of the argument: 1) *a priori* knowledge of the antibody structure is not required to practice the instant invention; 2) since a catalytic antibody is a species of the genus "antibody", the applicants had the invention in their possession at the time of filing; and 3) the catalytic antibodies of the present invention are defined by their selective and specific binding to targets chosen by the artisan practicing the invention.

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The applicants have demonstrated that a library produced by the claimed process contains antibodies that bind a particular transition state hapten (NPN). (See, e.g., Figure 13 described in detail at page 10, lines 9-18, and Example 18, particularly 18C, and pages 84-85 of the specification which were subsequently shown to have the predicted catalytic activity.) (See Sastry *et al.*, *Catalytic Antibodies*, 1991, Ciba Foundation, 159, pp. 145-155 (Exhibit A) of which one of the authors is an inventor of the presently claimed subject matter.)

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Thus, the method of the present invention eliminates any need for the kind of structure-function information discussed by the Examiner other than the fact that the polypeptides are V_H and V_L polypeptides which are provided by the described methods and which in combination have catalytic activity. If in fact such information becomes desirable, one could obtain an antibody which binds to a target, and has a catalytic activity using the methods of the present invention and then analyze the structure of the antibody so obtained to

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ascertain any structure function relationship that might be desired. However, such information is demonstrably unnecessary to practice the presently claimed invention.

Furthermore, there are many cases when the U.S. Patent Office has granted generic claims for antibodies to novel targets with no requirement that the detailed structure of the antibody to such a target is described. For example, U.S. patents 6,548,641; 6,545,130; 6,545,128 and 6,521,228 (attached as Exhibits B, C, D and E) claim antibodies without any description of structural features of the antibodies. Rather, the antibodies are defined by reference to the type of target they act upon and not by reference to any structural feature. The Examiner is invited to note especially that claim 28 of U.S. patent 6,521,228 claims not only an antibody which binds a target but also exerts a functional effect in doing so. There is no requirement under U.S. law to define the specific structural features of an antibody when those of skill in the art are capable of generating any number of antibodies which can differ structurally, but all of which have the feature of binding a particular defined class of targets. Still further, the claims of the present application provide more structural information than the claims of the cited patents: by virtue of its recitation of the of a V_H and V_L polypeptide which in combination have a catalytic activity.

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description

In view of the foregoing arguments, the applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph, is improper and should be withdrawn.

C. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

The Examiner has rejected claims 22-29 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner alleges that "the instant claims are drawn to [a] V_H and V_L polypeptide and that "it is not clear if a single polypeptide comprising both a V_H and V_L segment is encompassed, or a combination of two polypeptides as in an antibody or functional fragment thereof, such as an F_{ab}." In other words, the Examiner raises a question whether V_H and V_L polypeptide has a catalytic activity by themselves or whether it is only a dimer of two V_H and V_L polypeptides or a fully assembled antibody that has such a catalytic activity.

The present claims clearly require a functional relationship between the V_H and V_L polypeptides which is readily understood by those of ordinary skill in the art. Physical attachment of V_H to V_L to one another is not required. It is known for example that antibody binding function can be retained in the F_V format wherein the V_H and V_L are not necessarily

So, question
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linked. Therefore, the claims are not limited to whole antibodies or F_{ab} fragments of antibodies.

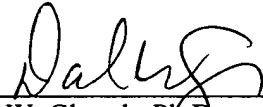
The applicants respectfully submit that the instant claims particularly point out and distinctly claim the subject matter which the applicants regard as the invention. In view of the foregoing amendments and arguments, the applicants request that the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Conclusion

The applicants submit that claims 22-29 are in condition for allowance and early notification thereof is solicited. The Commissioner is hereby authorized to charge any additional fees which may be required in the Application to Deposit Account No. 54-1214.

Respectfully submitted,

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Attachment

Example A. U.S. patent 6,548,641

1. An isolated antibody which binds to a polypeptide consisting of the amino acid sequence of SEQ ID NO:5, amino acid residues 6-101 of SEQ ID NO:5, amino acid residues 112-215 of SEQ ID NO:5, amino acid residues 216-275 of SEQ ID NO:5, amino acid residues 276-517 of SEQ ID NO:5 or amino acid residues 518-593 of SEQ ID NO:5.

Comment: No description of any structural feature of the antibody - merely defined by reference to its target.

Example B. U.S. patent 6,545,130

1. A monoclonal antibody which does not bind to Mycobacterium avium and which binds to the same Mycobacterium tuberculosis surface epitope as the monoclonal antibody produced by hybridoma cell line H-9d8 having ATCC Accession No. HB-12364.

Comment: Claim is to any antibody which binds to an epitope, the epitope being defined not in structural terms but only in functional terms. The antibody can be any structure which binds to the epitope, not merely the deposited antibody.

Example C. U.S. patent 6,545,128

3. An isolated antibody, or antigen-binding fragment thereof, which specifically binds to a Bax inhibitor protein selected from the group consisting of SEQ TD NO: 3 and SEQ ID NO: 6.

Comment: As with other applications, the antibody is claimed by reference to its functional properties, i.e. the ability to define a class of targets. No specific description of the structure of any species of antibody in the patent.

Example D. U.S. patent 6,521,228

26. An antibody that binds a fragment of the TRAIL protein of SEQ ID NO:2, wherein the N-terminal amino acid of said fragment is selected from residues 39 to 124 of SEQ ID NO:2, and the C-terminal amino acid of said fragment is selected from residues 276 to 281 of SEQ ID NO:2.

27. An antibody of claim 26, wherein said antibody is a monoclonal antibody.

28. An antibody of claim 26, wherein the antibody inhibits TRAIL-mediated apoptosis of a target cell.

Comment. Another example of claims to an antibody per se defined not structurally but by its ability to bind a target (Claim 26) and to exert a particular functionally defined result on its target (Claim 28).

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Screening combinatorial antibody libraries for catalytic acyl transfer reactions

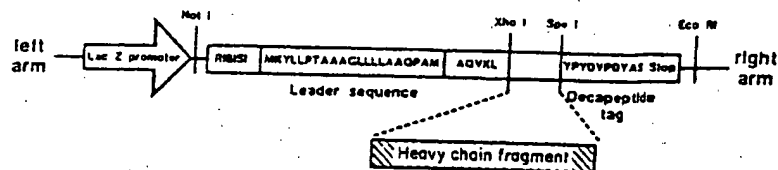
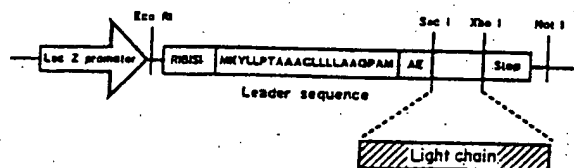
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Abstract. A bacteriophage λ vector system for the expression of Fab fragments from the mouse antibody repertoire in *Escherichia coli* has been described. We have used this system to generate a catalytic antibody from a combinatorial antibody library. Monoclonal antibody 43C9 was raised against a transition state analogue of the hydrolysis of carboxamide. mRNA from hybridoma cells expressing this antibody was cloned into phage λ and clones that expressed the mRNA for either the heavy or the light chain of the antibody were isolated. These individual libraries were then crossed to generate a combinatorial library in which clones coexpressed the heavy and light chains. This library was screened for antibodies/Fab fragments that bound to the original antigen with high affinity. DNA sequencing showed that these fragments were the same as those in antibody 43C9. Three different clones were found to catalyse the hydrolysis of carboxamide. More efficient expression vectors and improved screening techniques should lead to the isolation of many more catalytic antibodies from combinatorial antibody libraries.

1991 *Catalytic antibodies*. Wiley, Chichester (Ciba Foundation Symposium 159) p 145-155

Monoclonal antibodies are used extensively in various fields of biology and medicine. Some important applications include the investigation of cellular mechanisms, the isolation of interferons, cancer research, clinical diagnosis and gene product analysis. The generation of monoclonal antibodies with specific catalytic functions is an emerging technology that combines the high specificities of antibodies with chemical catalysis. A number of reactions have been successfully catalysed by monoclonal antibodies (for review see Lerner & Benkovic 1988). The production of homogeneous antibodies for catalysis is entirely dependent on the hybridoma technology; but this is an inefficient method

Heavy chain vector - λ Hc2Light chain vector - λ Lc1

Combinatorial construct

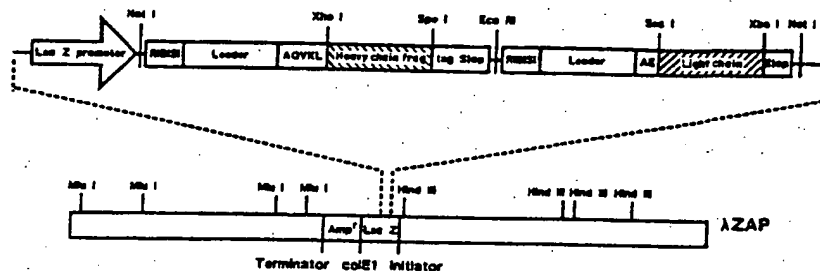


FIG. 1. Combinatorial bacteriophage λ vector system for expression of Fab antibody fragments. The LC1 vector is for cloning PCR products of mRNAs that code for κ light chains; the HC2 vector is for cloning PCR products of mRNAs coding for heavy chain Fd sequences. The combinatorial constructs that can express Fab fragments are generated by cutting light and heavy chain DNA at the antisymmetric *Eco*RI site of each vector, followed by religation of the resulting arms.

for surveying the immunological repertoire and limits the number of catalysts that can be obtained. We have developed a system using bacteriophage λ to clone and express a combinatorial library of Fab fragments of the mouse antibody repertoire in *Escherichia coli* (Fig. 1) (Sastry et al 1989, Huse et al 1989). The system allows rapid and easy identification of monoclonal Fab fragments in a form suitable for genetic manipulation. However, it remains to be shown that such combinatorial libraries can be used to produce catalytic Fab

fr: ents. In this paper we demonstrate the generation of a catalytic antibody from a combinatorial antibody library.

Using the λ phage system we generated an Fab combinatorial library from the spleen of a mouse immunized with phosphoramidate 1 (NPN), a transition state analogue for the hydrolysis of carboxyamide substrate 2 (Fig. 2). Screening the library with the antigen, NPN, linked to bovine serum albumin (NPN-BSA) resulted in the identification of a number of Fab fragments that bound to the antigen in a competitive manner. To find efficient catalysts for the hydrolysis of the nitroanilide 2, we screened the Fab combinatorial library directly for catalysis. The induced phage libraries were incubated with nitrocellulose filters saturated with the substrate, or the substrate was added directly to agar containing cells infected with the phage before they were poured onto a plate. Unfortunately, these approaches were unsuccessful because of the chemical nature of the reaction as well as the limited amount of Fab that is secreted by the phage molecules. It has previously been observed that catalysis of hydrolysis of the amide 2 occurs at 37 °C with high concentrations of an antibody (Janda et al 1988).

The high concentrations of antibody required for catalysis are difficult to achieve directly on the phage surface. Also, the product of the hydrolysis, *p*-nitroaniline, is diffusible and is hard to observe either directly on phage

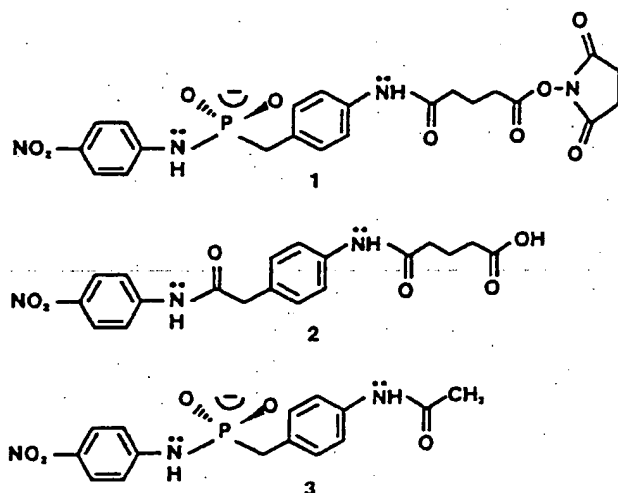


FIG. 2. The transition state analogue phosphoramidate 1 (NPN) which was used to induce antibodies that hydrolyse the carboxyamide substrate 2. The phosphoramidate functionality mimics the stereoelectronic features of the transition state for hydrolysis of the amide bond. The transition state analogue 3 is an inhibitor of the reaction.

plaques or on nitrocellulose filters. Because of these practical limitations, we decided to screen initially for Fab fragments that bound to NPN and then for those that showed catalytic activity. As an essential first step, we cloned and expressed a monoclonal antibody (43C9) that catalyses the amide hydrolysis in the phage system (Janda et al 1988). Besides being an internal control, the expression of the monoclonal antibody in phage also allows the study of its structure and mechanism of catalysis. Mutagenesis and chain-exchange experiments can be easily performed on the cloned antibody to improve its catalytic activity.

Methods

Total RNA from 10^7 43C9 hybridoma cells was isolated as described (Chomczynski & Sacchi 1987). The mRNAs were purified on an oligo dT column, then amplified using the polymerase chain reaction to obtain separate pools of heavy and light chain DNA (Sastry et al 1989, Huse et al 1989). Amplification of heavy chain DNA was performed with eight different 5' primers and a 3' primer specific for the IgG2b isotype. Light chain DNA was similarly amplified with five 5' primers and a κ chain-specific 3' primer. Heavy and light chain libraries were generated in phage λ and crossed to obtain an Fab combinatorial library (Huse et al 1989). This library was then screened with NPN-BSA labelled with ^{125}I and Fab fragments that bound the antigen were identified (Huse et al 1989). These Fab fragments were excised using helper phage (M12 mp8) and McBlue cells and plated on LB/ampicillin plates (Short et al 1988). Colonies on the plates represented the excised plasmid carrying the cloned heavy and light chain pieces.

Individual clones were grown up and their protein products isolated using an affinity column made from anti-(Fab')₂ coupled to Sepharose beads. Purified Fab was dialysed for 4–6 hours against ATE (Aces, Tris, ethanolamin) buffer, pH 9.0, concentrated to 1–3 μM solution, and used for catalysis. Catalysis was performed at 37 °C in ATE buffer at pH 9.0 with the 1–3 μM Fab solution and a saturating amount (1 mM) of substrate 2. Sequencing of the positive clones was as described by Sanger et al (1977).

Results

PCR amplification of heavy and light chain DNA resulted in bands of about 700 bp as analysed by agarose gel electrophoresis. A number of different primers were used for amplification from the hybridoma cells, because these may contain other non-functional heavy or light chains and restricted amplification may result in the cloning and expression of the wrong chains. To avoid this problem, we pooled the amplified DNA from the heavy and the light chains, then cloned each pooled fraction into the expression vector. Cloning of heavy chains resulted in 2×10^6 recombinants; the light chain library contained 5×10^5 recombinants.

Screening of the heavy chain recombinants with an antibody raised against a conserved 10 amino acid sequence in the heavy chain showed that 90% of these were expressing the decapeptide and therefore the heavy chain. Anti- κ antibody screening of the light chain library indicated that 60% of the clones were expressing κ light chains. The combinatorial library consisting of 2×10^7 recombinants was screened with the anti-decapeptide and anti- κ antibodies; 65% of the clones coexpressed heavy and light chains.

The Fab library (3000 plaques/plate) was then screened with iodinated NPN-BSA and positive clones were identified after a three-day exposure. Fragments that bound the antigen (binders) were identified at a frequency of 1/200; this relatively low frequency may be due to the presence of non-functional heavy and light chains in the Fab library. Ideally, amplification of the hybridoma RNA with specific 5' heavy and light chains should generate Fab fragments that bind at a much higher frequency.

The DNA sequences of the binders were obtained to identify the clone that exactly represents the monoclonal catalytic antibody 43C9. Comparison of the light chain deduced N-terminal amino acid sequence of antibody 43C9 and the deduced amino acid sequences of ten of the binders indicated that five of the clones (8a11, 8a12, 8a1, 7a2, 7a4) had the correct light chain. Three of these clones (8a1, 8a11, 8a12) were identical and differed from each of the other two (7a2, 7a4) by a single amino acid in the framework region. All the clones had the same heavy chain sequence; comparison with the N-terminal sequence of the authentic antibody was not possible because its N-terminus is blocked.

Purified Fab from each of the ten clones described above was assayed for catalytic activity; 8a11, 7a2 and 7a1 hydrolysed amide 2 at a rate clearly above the background rate (Fig. 3). The reaction was inhibited completely by the addition of transition state analogue 3, 20 μ M. This indicated that the observed catalysis was exclusively due to the Fab. SDS-PAGE of the catalytic recombinant Fabs showed a single species at 50 kDa. Reducing conditions gave a doublet at 25 kDa, indicative of a single pure Fab fragment. Because of the limited amount of Fab produced in our system, detailed kinetic analysis has not been possible. Overexpression of the catalytic Fab is currently being sought, to facilitate the kinetic studies.

Discussion

The bacteriophage λ vector system developed for the expression of Fab fragments is ideally suited for studying the structure and mechanism of any desired monoclonal antibody. We have successfully expressed a monoclonal catalytic Fab in this system and have shown that it retains the ability to catalyse a specific amide hydrolytic reaction.

Future studies will be aimed at identifying more binders from the library which also display catalytic activity. The success of these will hinge upon our ability

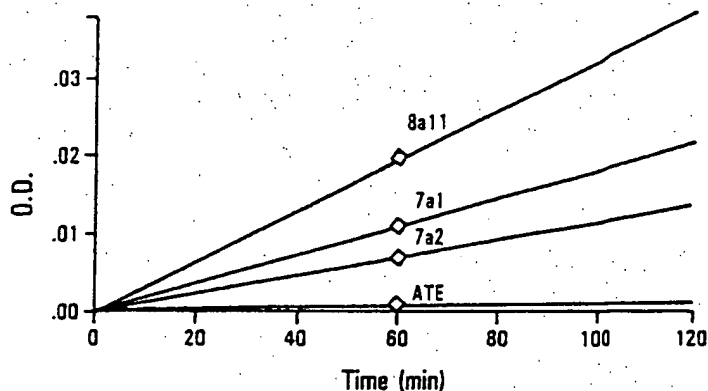


FIG. 3. Hydrolysis of carboxamide 2 by Fab clones 8a11, 7a2 and 7a1. Hydrolysis was carried out at 37 °C with 2 μ M antibody, 1 mM substrate in ATE buffer, pH 9.0. The differences in the observed rates seen for each clone probably reflect inaccuracies in protein concentration determination rather than clone differences. The background hydrolysis was measured with the substrate alone; in all cases the reaction was monitored at 405 nm.

to obtain a better system for expressing the protein, possibly utilizing Summer's baculovirus system (Smith et al 1983). More efficient screening for catalytic antibodies might be achieved via a genetic selection process.

Finally, a general solution to the antibody catalysis of a peptide bond may be obtained using the phage technology presented. Recently, we have constructed a single chain antibody with a coordination site for metals (Iverson et al 1990). When this site is incorporated into the light chain of an Fab fragment, a bound metal ion could act as a hydrolytic cofactor when properly aligned with a heavy chain which binds a small peptide sequence. The possibility of such a reaction appears remote; however, by taking advantage of the large numbers and combinations available through the combinatorial library, opportunities for success are within reach.

References

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DISCUSSION

Hansen: The exact placing of an amino acid is critical for enzyme catalysis. Do you have a sense, perhaps from Sargeson's work (Buckingham et al 1970), of how precise one has to be in orienting a carbonyl group near the metal ion to see catalysis?

Lerner: I don't know. They were basically looking at an intramolecular situation, because the substrate was directly bound to an open site on the coordination complex.

Martin: Another structural detail to consider is the geometry of the antibody's metal-binding ligands. A slight difference in the relative positions of metal-binding amino acid side chains could have a dramatic effect on the catalytic efficiency of the antibody. The coordination geometry of metals in natural enzymes is often distorted: for example, the tetrahedral geometry of cobalt-substituted carboxypeptidase A is markedly irregular compared to simple tetrahedral complexes of cobalt such as cobalt tetrachloride. In their entatic state hypothesis, Vallee & Williams (1968) proposed that the distorted coordination geometry is a critical feature of metalloenzymes in that it causes the metal to be unusually reactive—in their terms 'poised for catalysis'.

Lerner: Isn't that flying in the face of results from a great number of coordination complex experiments?

Jencks: Ground state strain of that kind can change the properties of the ions and the ligands and the metal, certainly; but to say that the ground state strain or distortion directly influences the transition state is wrong. It may provide a system which has a proper pK or oxidation potential or whatever, that will lead to a transition state more readily, and this might be done better with another metal that has a different size and a different potential, but it doesn't relate directly to the stability of the transition state.

Martin: If the enzyme or antibody binds a metal with tetrahedral geometry, say by three amino acid side chains and a reactive water molecule, the effect of the distorted coordination geometry might be to fine tune the pK of the metal-bound water molecule, thereby making it more reactive.